REMARKS

Upon entry of this amendment, claims 38 and 41-46 will be pending. Claims 38 and 44 have been amended herein. Claims 39 and 40 have been canceled without prejudice to prosecution at a later date. Claims 45 and 46 have been added. No new matter has been introduced by way of this amendment.

The specification has been amended to reflect the correct claim of priority. The priority claim contained a typographical error in referring to Application Serial No. 08/471,491 which is corrected herein. The specification also has been amended to properly reference the proprietary nature of the trademarks cited therein and to reflect the correct address of the American Type Culture Collection. Applicants submit that no new matter has been introduced by way of this amendment.

Applicants additionally submit that the amendment submitted August 6, 2002 does not contain new matter. Support for the added material "initiation sites. The expression of a portion of the CAI antigen by clone 57/D suggests," which phrase was inadvertently omitted from the preliminary amendment submitted August 2, 2001, is located on page 52, lines 31-38 of the specification as filed. Withdrawal of the objection is respectfully requested.

Applicants respectfully traverse the restriction requirement for the reasons already of record.

Preliminarily, Applicants note with appreciation the acknowledgment of the preliminary amendments filed August 2, 2001, February 27, 2002, and August 6, 2002. Applicants further note with appreciation entry of the sequence listing and return of the

initialed Information Disclosure Statement.

Applicants have submitted formal drawings to the Drawing Review Branch.

I. Claims 38 and 44 are provisionally rejected for alleged double patenting.

Claim 44 is provisionally rejected for alleged obviousness-type double patenting over claims 63-66, 72-75, 84-86, and 93-101 of the copending application, Serial No. 09/360,934. Claims 38 is provisionally rejected for alleged obviousness-type double patenting over claims 63-66, 75, 84-86, 93, 94, and 97-101 of the copending application, Serial No. 09/360,934. Applicants disagree.

In determining whether a nonstatutory basis exists for a double patenting rejection, the issue is whether any claim in the application defines an invention that is merely an obvious variation of an invention claimed in the patent. When the claimed subject matter is patentably distinct from the subject matter claimed in a commonly owned patent, a double patenting rejection is improper. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). Any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination (*In re Braat*, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991)); however, a double patenting rejection must rely on a comparison of only the claims. *See* MPEP § 804, part III. Applicants submit that claims 38 and 44 recite inventions that are not mere obvious variations of the inventions encompassed by the claims of Application Serial No. 09/360,934.

Nonetheless, without conceding the obviousness of claims 38 and 44 in view of the cited claims of the copending application, Applicants submit that a terminal disclaimer over Application Serial No. 09/360,934 will be filed upon receipt of an indication of allowability

of the cited claims in that case and of claims 38 and 44 in the present case.

II. The claims as amended satisfy 35 U.S.C. § 112, second paragraph.

Claim 38 is rejected for alleged indefiniteness in the recitation of a polypeptide "comprising SEQ ID NO:3." Applicants have amended claim 38 to recite a polypeptide "comprising the amino acid sequence of SEQ ID NO:3." Accordingly, Applicants request withdrawal of the rejection.

Claims 38 and 44 are rejected for alleged indefiniteness in the recitation of "CT." Claims 38 and 44 have been amended to recite "cytotoxin." Accordingly, Applicants request withdrawal of the rejection.

Claim 39 is rejected for alleged indefiniteness in the recitation of the phrase "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity." Applicants disagree. Nonetheless, Applicants have canceled claim 39 without disclaimer or prejudice.

Claims 38 and 44 are rejected for alleged indefiniteness in the recitation of the phrase "substantially no toxicity" or "substantially reduced toxicity." Applicants disagree. As recently stated by the Federal Circuit,

> Patent documents are written for persons familiar with the relevant field; the patentee is not required to include in the specification information readily understood by practitioners, lest every patent be required to be written as a comprehensive tutorial and treatise for the generalist, instead of a concise statement for persons in the field . . . . The question is not whether the word "substantially" has a fixed meaning . . . but how the phrase would be understood by persons experienced in this field . . . upon reading the patent documents.... Expressions such as "substantially" are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations

> that may be appropriate to secure the invention. Such usage may well satisfy the charge to "particularly point out and distinctly claim" the invention, 35 U.S.C. §112, and indeed may be necessary in order to provide the inventor with the benefit of his invention. In *Andrew Corp. v. Gabriel Elecs.* Inc., 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988) the court explained that usages such as "substantially equal" and "closely approximate" may serve to describe the invention with precision appropriate to the technology and without intruding on the prior art. The court again explained in *Ecolab Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1367, 60 USPQ2d 1173, 1179 (Fed. Cir. 2001) that "like the term 'about,' the term 'substantially' is a descriptive term commonly used in patent claims to 'avoid a strict numerical boundary to the specified parameter,'" quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217, 36 USPQ2d 1225, 1229 (Fed. Cir. 1995).
>
> It is well established that when the term "substantially" serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite.

Verve, LLC v. Crane Cams, Inc., 311 F.3d 1116, 1119-1120 (Fed. Cir. 2002).

The term "substantially" is a term of art routinely used in the field of biotechnology. Applicants submit herewith a Declaration of Dr. Giuseppe Del Giudice. Dr. Del Giudice is a medical doctor with approximately 15 years experience in vaccine development at the time of execution of the declaration. The Declaration of Dr. Del Giudice was previously submitted in connection with prosecution of Application Serial No. 09/360,934, the parent application of the present application having an identical disclosure. During prosecution of that application, a rejection under 35 U.S.C. § 112, second paragraph which mirrored that presently asserted was made to the solicited claims. Dr. Del Giudice attested that the term "substantially" is clearly understood by those of ordinary skill in the art. *See* Del Giudice Declaration, paragraph 7.

Indeed, numerous biotechnology patents have recently issued having claims including the term "substantially." *See, e.g.,* U.S Patent No. 6,495,667 (reciting in claim 3 methods of

making a binding composition by administering to an animal "substantially pure and isolated" polypeptides); U.S. Patent 6,492,499 (claiming compositions comprising "substantially purified human PAP-2 protein"); U.S. Patent No. 6,491,920 (claiming isolated nucleic acid sequences encoding a protein comprising an amino acid sequence having "substantially the same structure and biological activity as the amino acid sequence of Formula I"); and U.S. Patent 6,489,155 (reciting isolated genes having a DNA sequence encoding a polypeptide having a degrading activity which degrades a sulfated-fucose-containing polysaccharide "constituting saccharide substantially free from uronic acid" and "substantially incapable of being degraded"). Accordingly, Applicants submit that one having ordinary skill in the art of biotechnology would understand the metes and bounds of the invention as defined by claims 38 and 44. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

Claims 38, 39, and 44 are rejected for alleged indefiniteness in the recitation of the phrase "can induce." Applicants disagree. Preliminarily, Applicants note that claim 39 has been withdrawn herein without prejudice. To advance prosecution of the case, Applicants have amended claims 38 and 44 to recite polypeptides that are immunologically identifiable by antibodies that specifically react with *Helicobacter pylori* antigens. Support for these amendments is found throughout the specification as filed. For example, the specification discloses the preparation of antisera against the *Helicobacter pylori* cytotoxin and the use of the antisera to detect polypeptides immunologically identifiable with the *H. pylori* cytotoxin. *See, e.g.,* specification at 45, line 26 to 46, line 6.

Claim 39 is rejected for alleged indefiniteness in the recitation of the term "fragment." Applicants disagree. Nonetheless, to advance prosecution of the application, Applicants have

withdrawn claim 39 without prejudice.

Claim 40 is rejected for depending from an allegedly indefinite claim. Applicants disagree. Nonetheless, Applicants have withdrawn claim 40 without prejudice.

Applicants request reconsideration and withdrawal of the rejection.

III. Claims 39 and 40 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Claims 39 and 40 are rejected for alleged lack of written description. Applicants disagree. Nonetheless, to advance prosecution of the application, Applicants have withdrawn claims 39 and 40 without prejudice.

IV. Claims 38-40 and 44 are enabled by the specification in accordance with 35 U.S.C. § 112, first paragraph.

Claims 38-40 and 44 are rejected for alleged lack of enablement. Applicants disagree. Preliminarily, Applicants note that claims 39 and 40 have been withdrawn without prejudice or disclaimer to advance prosecution of the application.

The enablement requirement of 35 U.S.C. § 112, first paragraph, mandates that the specification teach those in the art how to make and use the claimed invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). The test of enablement is not whether any experimentation is necessary but, whether, if experimentation is necessary, it is undue. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404.

The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of nonenablement must be based on the evidence as a whole. *See id.* In order to make a rejection, the examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *See In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The burden then shifts to the applicant to provide persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See In re Brandstadter*, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973).

Applicants submit that the skilled artisan would be able to make and use the claimed invention using the application as a guide.

The Examiner alleges that the specification does not teach cytotoxin polypeptides that exhibit substantially no toxicity or have substantially reduced toxicity. Applicants respectfully disagree.

Preliminarily, Applicants have amended the claims to clarify that "toxicity" refers to "cytotoxicity" as supported in the specification. *See, e.g.,* Specification at 5, lines 35-39.

The Examiner alleges that the specification states that CT is cytotoxic in that it causes vacuolation and death of a number of eukaryotic cell types. The specification actually teaches that the *processed* 100 kDa polypeptide possesses cytotoxic activity. *See* Specification at 5, lines 31-39. "Cytotoxin," however, is defined in the specification to include the precursor protein having a molecular weight of 140 kDa and fragments and derivatives thereof. *See id.* The specification discloses a representative example in which the cytotoxicity of the cytotoxin is determined by measuring the vacuolizing activity of the polypeptide on HeLa cells. *See* Specification at 50. The specification also discloses methods for preparing and testing antisera against the cytotoxin. *See* Specification at 45, line 25 to 46, line 6.

Applicants submit herewith a Declaration of Dr. Giuseppe Del Giudice, which was previously submitted in connection with prosecution of Application Serial Number 09/360,934, wherein an enablement rejection under 35 U.S.C. § 112, first paragraph similar to the present rejection was asserted. Dr. Del Giudice attested that chemically inactivated and genetically detoxified toxins were known to those of skill in the art, as supported by Manetti et al. (*Infect. Immun.*, 63:4476-4480 (1995) (Del Giudice Declaration, Exhibit A)). *See* Del Giudice Declaration at paragraph 9. Further, protein fragments are easily generated by known techniques. *See id.* at paragraph 11. Additionally, according to Dr. Del Giudice, a determination of immunogenic polypeptide fragments and derivatives exhibiting substantially no cytotoxicity, such that they would be functional in the present claims, was and is routine in the art. *See id.* at paragraph 10. Indeed, *in vitro* vacuolation assays are routinely used to

determine the toxicity of the cytotoxin. *See id.* at paragraph 12 (citing Reyrat et al., *Mol. Microbiol.*, 34:197-204 (1999) (Del Giudice Declaration, Exhibit B)). Likewise, animal models are routinely used to study the effects of *H. pylori* infection *in vivo* and may be used to assess the cytotoxicity of a cytotoxin polypeptide. *See id.* at paragraph 13 (citing Krakowka et al., *Infect. Immunol.*, 55:2789-2796 (1987) (Del Giudice Declaration Exhibit C), Radin et al., *Infect. Immunol.*, 58:2606-2612 (1990) (Del Giudice Declaration Exhibit D), and Telford et al., *J. Exp. Med.*, 179:1653-1658 (1994) (Exhibit E)). Additionally, it is routine for one of skill in the art to perform an immunological assay to determine the immunogenicity of the cytotoxin polypeptides. *See id.* at paragraph 14.

Applicants note, however, that although a determination of the toxicity and immunogenicity of the cytotoxin polypeptides is routine to one of ordinary skill in the art, it would not have been obvious to one of skill in the art to have done so to arrive at the present claims absent Applicants' disclosure.

Nothing more than routine experimentation is required to determine the cytotoxin polypeptides that work in the invention in view of the examples provided in the application. That some experimentation may be required is not fatal; the question is whether the experimentation is undue. *See Wands*, 8 U.S.P.Q.2d at 1404. Even a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. *See id.* Using the application as a guide, one of ordinary skill in the art would have been able to determine which cytotoxin polypeptides are immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin and exhibit substantially no cytotoxicity or substantially reduced cytotoxicity.

The Examiner also has alleged that the prophylactic and therapeutic vaccines of the

invention are not enabled by the specification because the specification "lacks *in vivo* evidence demonstrating the prophylactic or therapeutic efficacy of the claimed vaccine with or without the second polypeptide, or any *in vitro* evidence that is predictive of, or correlative with prophylactic and therapeutic efficacy of the vaccine." Office Action at 11. Applicants disagree. Nonetheless, to advance prosecution of the application, Applicants have amended the claims to recite immunogenic compositions. The amendment is fully supported by the specification as filed. *See, e.g.,* Specification at 40, line 16 to 41, line 17.

Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

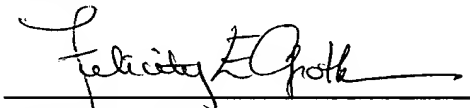
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

A "Version with Markings to Show Changes Made" is attached hereto.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at 215-557-5908.

Respectfully submitted,



Date: March 17, 2003

Felicity E. Groth
Registration No. 47,042

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Attachments

Version with Markings to Show Changes Made
Declaration of Giuseppe Del Giudice and Exhibits A-H

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the paragraph on page 1, following the heading "Cross-Reference to Related Applications" as follows:

-- This application is a continuation of U.S. Application Serial No. 09/360,934, filed July 26, 1999, now pending, which is a divisional of U.S. Application Serial No. [08/471,491] 08/466,662, filed June 6, 1995, now issued as U.S. Patent No. [6,090,611] 6,130,059, which is a divisional of U.S. Application Serial No. 08/256,848, filed October 21, 1994, now abandoned, which is a U.S national phase application of PCT/EP93/00472, filed March 2, 1993, [which also claims priority to] and PCT/EP93/00158, filed January 25, 1993[, both of which PCT applications claimed priority benefit of]. The instant application also claims the benefit of priority of Italian Application Serial No. FI 92 A 000052, filed March 2, 1992. PCT/EP93/00472 was published in English and PCT/EP93/00158 was abandoned prior to publication. The entire contents of each application is hereby incorporated by reference.--

Please amend the paragraph bridging pages 39, line 18 to page 40, line 9 as follows:

-- Preferred adjuvants to enhance effectiveness of the composition include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc.; (2) oil-in-water emulsion formulations (with or without other specific

immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (PCT Publ. No. WO 90/14837), containing 5% Squalene®, 0.5% Tween 80®, and 0.5% Span 85® (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalane, 0.4% Tween 80®, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene®, 0.2% Tween 80®, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (3) saponin adjuvants, such as Stimulon™ (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freunds Adjuvant (CFA) and Incomplete Freunds Adjuvant (IFA); (5) cytokines, such as interleukins (IL-1, IL-2, etc.), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition. Alum and MF59 are preferred.--

Please amend the specification on page 61, first paragraph to as follows:

-- The following materials were deposited on December 15, 1992 and January 22, 1993 by Biocine Sclavo, S.p.A., [the assignee of the present invention,] with the American Type Culture Collection, [12301 Parklawn Drive, Rockville, Maryland, phone (301) 231-5519] 10801 University Boulevard, Manassas, VA 20110-2209, under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for Purposes of

Patent Procedure.

For the cytotoxin protein (CT):

ATCC No. 69157 *E. coli* TG1 containing the plasmid TOXHH1

ATCC No. n/a *E. coli* TG1 containing the plasmid TOXEE1

For the CAI protein:

ATCC No. 69158 *E. coli* TG1 containing the plasmid 57/D

ATCC No. 69159 *E. coli* TG1 containing the plasmid 64/4

ATCC No. 69160 *E. coli* TG1 containing the plasmid P1-24

ATCC No. 69161 *E. coli* TG1 containing the plasmid B/1

For the heat shock protein (hsp):

ATCC No. 69155 *E. coli* TG1 containing the plasmid pHp60G2

ATCC No. 69156 *E. coli* TG1 containing the plasmid pHp605.--

In the claims:

Please cancel claims 39 and 40 without disclaimer or prejudice to later prosecution.

Please amend claims 38 and 44 as follows:

38. (amended) [A prophylactic or therapeutic vaccine] An immunogenic composition comprising an immunologically effective amount of a *H. pylori* [CT] cytotoxin polypeptide comprising the amino acid sequence of SEQ ID NO:3, which polypeptide: (i) is immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin [can induce the production of antibodies to *H. pylori*] and (ii) exhibits substantially no toxicity, or substantially reduced toxicity.

44. (amended) [A prophylactic or therapeutic vaccine] An immunogenic composition comprising an immunologically effective amount of a recombinantly produced *H. pylori* [CT] cytotoxin polypeptide comprising a fragment of an amino acid sequence of SEQ ID NO:3, wherein said recombinantly produced polypeptide (i) [can induce the production of antibodies to] is immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin and (ii) exhibits substantially no toxicity, or substantially reduced contribution to toxicity, and a pharmaceutically acceptable carrier.

Please add the following new claims 45 and 46:

45. (New) An immunogenic composition comprising an immunologically effective amount of a *H. pylori* cytotoxin polypeptide comprising the amino acid sequence of SEQ ID NO:3, which polypeptide: (i) is immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin and (ii) exhibits substantially no toxicity, or substantially reduced

toxicity, and a pharmaceutically acceptable carrier.

46. (New) An immunogenic composition comprising an immunologically effective amount of a recombinantly produced *H. pylori* cytotoxin polypeptide comprising a fragment of an amino acid sequence of SEQ ID NO:3, wherein said recombinantly produced polypeptide (i) is immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin and (ii) exhibits substantially no toxicity, or substantially reduced contribution to toxicity.